REMARKS

Claims 17-21 are in this application. The claims stand rejected under 35 U.S.C. § 103(a) as obvious over U.S. Pat. No. 5,268,292 (Robertson) in view of Bishop et al. and Andre et al. Applicants respectfully traverse and request withdrawal of the rejection.

Applicants respectfully assert that the instant invention is properly viewed as an improvement to the HAV preparation method taught by Andre et al. That is, the instant invention provides for a protease digestion step to facilitate, *inter alia*, removal of host nucleic acids by subsequent purification steps; protease digestion is not taught in Andre et al. The Examiner asserts that Robertson et al. "teach, subsequent to cell harvest, a method requiring trypsin treatment for purification of HAV . . . ". However, Robertson et al. also teach many other steps that are (surprisingly) not required to achieve highly purified preparations of HAV suitable for vaccine use. For example, Roberston et al. teach treatment of the 1 percent NP-40 soluble fraction of infected cells or media with DNase I prior to trypsin treatment (col. 5, lines 54-55). Subsequent to trypsin treatment, Robertson et al. teach treatment with SDS or SLS (i.e., ionic detergent treatment), a known protein disrupting and denaturing agent (col. 5, lines 59-61). In addition, Robertson et al. require a further viral aggregate disruption step by addition of 1M dibasic sodium phosphate (col. 5, lines 65-67), followd by a futher ionic detergent (SLS) treatment (col. 6, lines 1-3). One skilled in the art would not know which of the many steps taught by Robertson et al. to choose in order to improve the process taught by Andre et al.; i.e., there is no motivation in Robertson et al. to chose trypsin treatment as the sole feature that will improve the process of Andre et al.

Moreover, and in contrast to the Examiner's assertions, Bishop et al. does not provide this motivation and in fact could be seen as teaching away from the instant invention. Bishop et al. does not describe a method that comprises a trypsin digestion step to separate the virus from cells. Bishop et al. only utilize trypsin to detach cells from their growth substrate prior to any viral purification (see page 203, first full paragraph). In fact, Bishop et al. teach away from the use of trypsin by teaching the addition of FCS "to inhibit the trypsin". There is no other mention of the use of trypsin in Bishop's protocol. In fact, subsequent to non-ionic detergent extraction (NP-40), Bishop et al.'s next step is to add an ionic detergent (as in Robertson et al.). It is unlikely that trypsin, itself a protein, would be enzymatically active in a solution containing 2% SDS. Accordingly, one skilled in this art, following the teachings of Robertson and Bishop, would not chose trypsin treatment, but instead would chose an ionic detergent treatment, as the key feature to add to the protocol of Andre et al. (see Bishop et al., the sentence bridging pages

213 and 214: "By taking advantage of the stability of HAV in high concentrations of ionic detergents described here, it is possible to simultaneously purify and concentrate the virus in a single step, maximizing yields and minimizing time and costs.").

Finally, with respect to claims 20 and 21, Bishop et al. discourage one skilled in the art from using "gel-exclusion and ion-exchange chromatography, all of which may result in loss and/or dilution of the virus" (page 213, last paragraph).

In summary, the prior art does not teach or suggest the improvement represented by the instant invention over the methods disclosed in the art. There is no motivation to pick protease digestion amongst the many unique steps taught by Robertson et al. in order to improve the simple process taught by Andre et al. so as to achieve high levels of purity required for vaccine production (as an aside, there is no mention in Robertson et al. of the use of the products of their process as vaccine antigens). Moreover, Bishop et al. does not employ protease digestion at all and instead favors ionic detergent treatment to improve purity. Applicants thus respectfully assert that the instant invention is not obvious in view of the art and respectfully request withdrawal of the rejection.

Respectfully submitted,

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